UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,655	12/23/2005	Christian Pinset	CABHLP0002	3730

48947 7590 04/10/2008

ADELI & TOLLEN, LLP
1875 CENTURY PARK EAST, SUITE 1360
LOS ANGELES, CA 90067

EXAMINER	
HILL, KEVIN KAI	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
04/10/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,655	PINSET, CHRISTIAN	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 31-54* is/are pending in the application.

4a) Of the above claim(s) *34-45,47,50,51 and 53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,31-33,46,48,49,52 and 54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Group I, claim(s) 1 and 31-54, drawn to a method for a functional treatment of small muscles selected from the group comprising urethral sphincters, anal sphincters, eyelid muscles, muscles of the fingers, and muscles of the larynx, in a mammal, the method comprising administering myoblasts obtainable by culturing said myoblasts in a cell culture medium.

Applicant's response to the Requirement for Restriction, filed on January 22, 2008 is acknowledged.

i) The claims (claims 1, 32, 34-35, 38-45, 48, and 54) recite a plurality of alternative cell culture media components, and combinations thereof. Applicant is required under 35 U.S.C. 121 and 372 to elect a single disclosed cell culture media component species, or specific combination thereof, for prosecution on the merits to which the claims shall be restricted.

Applicant has elected the cell culture media components within which myoblasts are to be cultured is serum of animal origin, as recited in claims 1(i), 32(i), 48(i) and 54(i);

ii) Applicant is required under 35 U.S.C. 121 and 372 to elect a single disclosed alternative method step species, or specific combination thereof, for prosecution on the merits to which the claims shall be restricted.

Applicant has elected the alternative method steps recited in claims 46 and 52.

iii) Applicant is required under 35 U.S.C. 121 and 372 to elect a single disclosed small muscle tissue species for prosecution on the merits to which the claims shall be restricted.

Applicant has elected the small muscle tissue to be treated by the inventive cultured myoblasts is urethral sphincters, as recited in claims 48 and 54.

Election of Applicant's species was made with traverse on the grounds that it would not be an undue burden to search all the limitations of the claims.

Applicants' arguments have been fully considered but are not found persuasive. MPEP §803 states that "If the search and examination of all the claims in an application can be made without serious burden, the Examiner must examine them on the merits, even though they include claims to independent or distinct inventions."

In the instant case a serious burden exists since each limitation, directed to human sera, distinctly different method steps, and a plurality of distinctly different small muscles requires a separate, divergent, and non co-extensive search and examination of the patent and non-patent literature. For instance, a search and consideration of the prior art as it relates to animal sera or urethral small muscles would not be adequate to uncover prior art related to human sera and eyelid muscles, respectively.

Further, a search and examination of all the claims directed to both embodiments involves different considerations of novelty, obviousness, written description, and enablement for each claim. In view of these requirements, it is the Examiner's position that searching and examining all of the claimed limitations in the same application presents a serious burden on the Examiner for the reasons given above and in the previous Restriction Requirement.

It is noted that should Applicant traverse the species election requirement, that Applicant was invited to submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. Applicant has not done so.

The requirement is still deemed proper and is therefore made FINAL.

Upon further consideration of the claims, and as per the telephone conversation with Applicant's representative on January 3, 2008, the Examiner rejoins the species "a serum fraction of animal origin" with "a serum of animal origin" for examination purposes.

Claims 34-45, 47, 50-51 and 53 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 1, 31-33, 46, 48-49, 52 and 54 are under consideration.

Priority

This application is a 371 of PCT/FR03/03691, filed December 12, 2003 and claims benefit of the prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c). Acknowledgment is made of Applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) for the French application 02/15827 filed on December 13, 2002. A copy of the foreign patent application PCT/FR03/03691, published as WO 2004/055174 A1 on July 1, 2004 and a certified copy of French application 02/15827 are provided with the instant application.

Accordingly, the effective priority date of the instant application is granted as December 13, 2002.

The Examiner notes that English translations of the priority documents FR 02/15827 and PCT/FR03/03691 have not been filed with the instant application.

Information Disclosure Statement

Applicant has filed an Information Disclosure Statement on October 17, 2006 that has been considered. The signed and initialed PTO Form 1449 is mailed with this action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

1. **Claims 1, 31-33, 46, 48-49, 52 and 54 are rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

With respect to Claims 1, 48 and 54 (and dependent claims), the claims are vague and indefinite in that no step(s) in the claimed method refers back to or recapitulates the preamble of the claim. Applicants recite a method of treating small muscles, specifically urethral sphincters, but no step is recited that actually accomplishes the preamble. It is unclear if additional, undisclosed steps are a part of the claimed method and therefore the metes and bounds of the

claimed subject matter are unclear. Furthermore, the claims do not recite the location to where the myoblasts will be administered.

Dependent claims are included in the basis of the rejection because although they recite and encompass the method of treating small muscles, specifically urethral sphincters, they do not clarify when the method has been fulfilled.

With respect to claims 1, 48 and 54, the claims are indefinite for failing to recite the subject to whom the myoblasts are being administered (lines 2, 3 and 3, respectively). The Examiner respectfully suggests "administering to said mammal...", for example.

With respect to Claim 32, the claim recites the limitation "selecting cells and amplifying cells" in reference to the step of culturing myoblasts of claim 1. However, it is unclear what cell type the artisan is selecting for or against, nor is the selection means recited in the claim, e.g. chemical, morphological, antigenic marker, etc.

Furthermore, it is unclear if the cells that are being selected and amplified are the myoblasts of claim 1 or some other cell type because the claims embrace the step of differentiating cells to become myoblasts, and thus the claims embrace the culture of a plurality of cell types, including embryonic stem cells, for which one of ordinary skill in the art would know that each cell type has its own requirements for cell culture media components and conditions. Thus, the cells of claim 32 are broader in scope to the myoblasts of claim 1, and the artisan would not know the metes and bounds of the claimed method.

With respect to Claims 46 and 49, the claims recite the step of "performing cell differentiation". As a first matter, the claims are unclear because the methods of Claims 1 and 48, respectively, require the administration of myoblasts and the culturing of myoblasts, which are undifferentiated precursor cells to myocytes. If the artisan differentiates the myoblasts into myocytes prior to the administration method step of Claims 1 and 48, then the artisan is no longer administering myoblasts. As a second matter, the identity of the differentiated cell type is not disclosed. The art recognizes that adult skeletal muscle contains cells that are heterogeneous in terms of their differentiation status, expressing both genes specific to myogenic differentiation

and genes that are common to a number of differentiation pathways, and may therefore be considered 'stem cells' capable of differentiating into smooth muscle cells, neural tissue, haematopoietic cell, etc.. (Sinanan et al, Biol. Cell. 96(4):203-214, 2006). As a third matter, if the myoblasts are to be the intended 'differentiated cell', then the claims do not recite the cell type from which myoblasts are derived via the step of differentiation.

With respect to Claims 46 and 52, the claims recite the step of "performing a characterization on said myoblasts". However, the claims are indefinite because they do not recite those characteristics that inform the artisan of the metes and bounds of the claimed method. What genetic, phenotypic, developmental or morphological variable or trait is to be assayed and characterized?

Appropriate correction is required

2. **Claims 46 and 52 are rejected under 35 U.S.C. 112, second paragraph,** as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the step of thawing the frozen myoblasts prior to the administration step.

Appropriate correction is required

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. **Claims 1, 31-33, 46, 48-49, 52 and 54 are rejected under 35 U.S.C. 112, first paragraph**, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

The breadth of the claims is exceptionally large for encompassing methods of treating an enormous genus of anatomically distinct small muscles in need of treatment from an enormous genus of etiologically and pathologically distinct medical conditions in an enormous genus of mammals of any age, wherein the art recognize mammals to reasonably encompass some 5,500 species (including humans), distributed in about 1,200 genera, 152 families and up to 46 orders (en.wikipedia.org/wiki/Mammal, last visited March 21, 2007).

The inventive concept in the instant application is a cell culture medium composition and process to culture myoblasts capable of being used in cell and/or gene therapy products (pg 1, lines 5-8).

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

The specification discloses means of extracting muscle progenitor or stem cells from muscle tissue (pg 15, Example 1), culturing said cells in a defined media to amplify the muscle precursor cells (pgs 16-19, Examples 2-5), functional testing of human muscle precursor cells (pg 20, Example 6), improved cell freezing techniques (pg 22, Example 8), and selection/amplification protocols of muscle progenitor cells from biopsies (pg 24, Example 9).

However, the claims lack enablement because neither the claims nor the specification disclose how to administer the myoblasts so as to achieve a clinically meaningful and therapeutic result.

The State of the Prior Art, The Level of One of Ordinary Skill and The Level of Predictability in the Art

The claims are drawn to methods of cell therapy, which is a complex and unpredictable art.

Skuk et al (Exp. Neurology 155:22-30, 1999) teach that while very efficient myoblast transplantation grafts may be obtained in mice, poor results were observed after myoblast transplantation in dogs, monkeys, and humans. The poor results of myoblast transplantation in large animals were attributed to different problems like the absence of migration of transplanted cells and the high rate of mortality of transplanted myoblasts. In humans, voluminous muscles not conditioned by damaging agents were injected with a number of myoblasts significantly smaller for a large muscle and the injections were performed at greater distance from each other than in mice. Considering that myoblasts do not migrate into the muscle, their only possibility under these last conditions is to be incorporated into the fibers immediately next to the sites of injection (pg 27, col. 1, ¶s 2-3).

Animal research has demonstrated that immune-specific reactions against the donor cells and hybrid muscle fibers take place some days after myoblast transplantation (pg 22, col. 2, ¶3). Two other problems were also signaled as limiting the efficacy of myoblast transplantation: the absence of migration of myoblasts into the muscular tissue and the massive mortality of grafted cells after the transplantation (pg 23, col. 1, lines 1-5). The conditions in rodent experiments were largely different from those used in clinical trials and this could also explain the difference

of success of myoblast transplantation (pg 23, col. 1, ¶1). The art recognized a duality of results between rodent experiments and clinical trials as well as large animal models (pg 27, col. 1, ¶2).

Applicant's own post-filing work (Peyromaure et al, Urology 64(5): 1037-1041, 2004) teaches that:

> "The optimal number of muscle precursor cells to be injected into a recipient remains to be clarified in additional experiments (pg 1040, col. 2, ¶2). For clinical application, the critical question is to know whether muscle precursor cell transplantation in the lower urinary tract has only a bulk effect or could enhance sphincteric function. Information about functional characteristics and innervation of the implanted cells is lacking (pgs 1040-1041, joining ¶). Measurements of leak pressure is necessary to determine if true effect of implanted muscle precursor cells is better. Finally, there is no guarantee that the injected muscle precursor cells would incorporate into myofibers in elderly patients with urinary incontinence. It is possible that the elderly microenvironment is not as favorable. Clinical studies are needed to clarify this point. We acknowledge that muscle precursor cell injection into the normal striated urethral sphincter results in their incorporation in adult myofibers, as confirmed by our study. However, the possibility of myofiber regeneration and reinnervation after muscle precursor cell implantation in the urethral sphincter remains to be clarified." (pg 1041, col. 1, ¶ 1-2).

While the credentials of those of skill in the gene therapy art are impressive (M.D.s and Ph.D.s), their level of skill in actually practicing gene therapy for treatment of small muscles such as urethral sphincters is very low because they have not been successful in reducing cell therapy to practice. Given the above analysis of the factors which the courts have determined are critical in ascertaining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue and excessive experimentation in order to practice the claimed invention.

The Quantity of Any Necessary Experimentation to Make or Use the Invention

Thus, the quantity of necessary experimentation to make or use the invention as claimed, based upon what is known in the art and what has been disclosed in the specification, will create an undue burden for a person of ordinary skill in the art to demonstrate that myoblasts may be used to functionally treat an enormous genus of anatomically distinct small muscles, including urethral sphincters, in need of treatment from an enormous genus of etiologically and pathologically distinct medical conditions in an enormous genus of mammals of any age. This is because the artisan would have to essentially invent for themselves a determination of the frequency and location of the myoblasts to be implanted into the target tissue, the optimal number of myoblasts (myoblast-to-muscle volume ratio) to be transplanted, means of enhancing the survivability of the transplanted myoblasts, and means of overcoming or avoiding immune rejection of the donor myoblast cells and hybrid muscle fibers. One of skill in the art would need to rely solely upon the teachings of the specification for guidance in practicing the claimed invention because the prior art, including Applicant's post-filing art, teach that such obstacles have not been solved so as to achieve clinically and therapeutically meaningful results. However, the specification does not provide the requisite guidance for the practice of the claimed invention.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. **Claims 1, 31-33, 48 and 54 are rejected under 35 U.S.C. 102(b)** as being anticipated by Chancellor et al (Neurourol. and Urodyn. 19:279-287, 2000).

Chancellor et al teach a method of functionally treating urethral sphincters in a rat comprising the step of administering myoblasts obtained by culturing said myoblasts in a cell culture medium comprising serum of animal origin (pg 281, ¶2). The myoblasts were selected and amplified *in vitro* (pgs 280-281) in cell culture media comprising DMEM (also known in the art as Dulbecco's Modified Eagle's Medium).

With respect to the 'functionally treating' limitation, Chancellor et al teach that the approach for treatment is myoblast injection, which should "build up" and improve the urinary sphincter (pg 280, ¶2), wherein the formation of myotubes by the myoblasts is evident. Myotubes are capable of contraction and can survive for a long period in a stable fashion (pg 282, ¶1). Chancellor et al suggest that these results support the hypothesis that myoblast injection is a potential treatment for stress urinary incontinence and impaired detrusor contractility. The injection of the myoblasts in the bladder and urethral walls did not lead to any adverse effects (pg 283).

The myoblasts obtained by the culturing method disclosed in the instant specification and as claimed are determined to be a product-by-process claim. The recitation of process limitations in claims 1, 32, 48 and 54 are not viewed as positively limiting the claimed product myoblast absent a showing that the process of making recited in the claims imparts a novel or unexpected property to the claimed product, as it is assumed that equivalent myoblast products are obtainable by multiple routes. The myoblasts of Chancellor et al are structurally and functionally indistinguishable from the myoblasts of the instant application. The burden is placed upon the Applicants to establish a patentable distinction between the claimed and referenced products. The method in which the myoblasts were produced is immaterial to their patentability.

"Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior

product was made by a different process." *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP §2113.

In the instant claims, the claims recite "obtainable by culturing said myoblasts in a cell culture medium comprising serum of animal origin". Absent evidence to the contrary, the recitation "obtainable by...." is not considered to further limit the invention.

Thus, Chancellor et al anticipate claims 1, 31-33, 48 and 54.

5. **Claims 1, 31-33, 46, 48-49, 52 and 54 are rejected under 35 U.S.C. 102(e)** as being anticipated by Chancellor et al (U.S. Patent 6,866,842).

Chancellor et al disclosed a method treating urinary incontinence (col. 9, line 9) or enhancing urinary sphincters (col. 9, line 58), the method comprising the administration of myoblasts or muscle-derived stem cells. Primary myoblasts were harvested and extracted from muscle tissue, and cultured in cell culture media comprising animal sera (col.s 24-25, joining ¶), whereupon the myoblasts were assayed for desmin expression (col. 49, line 29-col. 50, line 18). The myoblasts were cultured *in vitro* and preserved their ability to differentiate, e.g. by expressing desmin, forming colonies of myotubes (col. 11, lines 8-10). Chancellor et al disclose that substances, e.g. bFGF, which enhance myoblast proliferation and differentiation *in vitro* may also increase muscle regeneration *in vivo* and prevent the development of scar tissue formation (col. 46, lines 20-23, lines 50-64; col. 47, Table 4). The cultured myoblasts may be frozen and stored indefinitely for possible future use (col. 59, lines 10-11).

The myoblasts obtained by the culturing method disclosed in the instant specification and as claimed are determined to be a product-by-process claim. The recitation of process limitations in claims 1, 32, 48 and 54 are not viewed as positively limiting the claimed product myoblast absent a showing that the process of making recited in the claims imparts a novel or unexpected property to the claimed product, as it is assumed that equivalent myoblast products are obtainable by multiple routes. The myoblasts of Chancellor et al are structurally and functionally indistinguishable from the myoblasts of the instant application. The burden is placed upon the Applicants to establish a patentable distinction between the claimed and referenced products. The method in which the myoblasts were produced is immaterial to their patentability.

"Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP §2113.

In the instant claims, the claims recite "obtainable by culturing said myoblasts in a cell culture medium comprising serum of animal origin". Absent evidence to the contrary, the recitation "obtainable by...." is not considered to further limit the invention.

Thus, Chancellor et al anticipate claims 1, 31-33, 46, 48-49, 52 and 54.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. **Claim 1, 31-32, 46, 48, 52 and 54 are rejected under 35 U.S.C. 102(a)** as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Chancellor et al (Neurourol. and Urodyn. 19:279-287, 2000) in view of Yiou et al (BJU International 89(3):298-302, 2002), Yokoyama et al (Urology 57:826-831, 2001) and Sanberg et al (U.S. Patent 5,942,437).

Determining the scope and contents of the prior art.

Chancellor et al teach a method of functionally treating urethral sphincters in a rat comprising the step of administering myoblasts obtained by culturing said myoblasts in a cell culture medium comprising serum of animal origin (pg 281, ¶2). The myoblasts were selected and amplified *in vitro* (pgs 280-281).

With respect to the 'functionally treating' limitation, Chancellor et al teach that the approach for treatment is myoblast injection, which should "build up" and improve the urinary sphincter (pg 280, ¶2), wherein the formation of myotubes by the myoblasts is evident.

Chancellor et al do not teach the method to comprise the steps of:

i) performing cell extraction from muscle tissues; and

ii) harvesting and separating the cells obtained from said cell extraction.

However, at the time of the invention, Yiou et al taught a method of functionally treating urethral sphincters in a mouse comprising the step of administering autologous myoblasts obtained by culturing said myoblasts in a cell culture medium. The muscle precursor cells were enzymatically harvested from striated muscles prior to transplantation, wherein the muscle mass was kept in growth medium for two days, and the dissociated cells were resuspended in growth medium (pg 299, col. 1, ¶2; Figure 1). The myoblast autograft cells accelerated sphincter muscle repair, as shown by a higher myofiber diameter and number.

Neither Chancellor et al nor Yiou et al teach the method to comprise the steps of:

iii) performing cell differentiation before, during or after cell amplification;

iv) carrying out a functionality test on the suitability of the myoblasts for forming colonies; and

v) performing a characterization on said myoblasts.

However, at the time of the invention, Yokoyama et al taught a method of functionally treating urinary incontinence in a mouse comprising the step of administering skeletal muscle-derived cells comprising satellite cells, an art-recognized myoblast, obtained by cell extraction from primary muscle tissue, harvesting and separating the cells obtained from said cell extraction, culturing said cells in a cell culture medium comprising serum of animal origin, carrying out a functionality test on the suitability of the myoblasts for forming colonies, and performing a characterization on said myoblasts, e.g. desmin staining and forming myofibers, (pg 827, col. 1, Purification).

Neither Chancellor et al, Yiou et al nor Yokoyama et al teach the method to comprise the step of:

vi) freezing the myoblasts.

However, at the time of the invention, Sandberg et al disclosed means of cryopreserving myoblasts (e.g. col. 6, lines 10-23, 29, 51-65).

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as doctors, scientists, or engineers, possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in anatomy, cell extraction from tissue, methods of cell tissue culture, propagation and storage, and cell transplantation into a host subject. Therefore, the level of ordinary skill in this art is high.

The myoblasts obtained by the culturing method disclosed in the instant specification and as claimed are determined to be a product-by-process claim. The recitation of process limitations in claims 1, 32, 48 and 54 are not viewed as positively limiting the claimed product myoblast absent a showing that the process of making recited in the claims imparts a novel or unexpected property to the claimed product, as it is assumed that equivalent myoblast products are obtainable by multiple routes. The myoblasts of the prior art are structurally and functionally indistinguishable from the myoblasts of the instant application. The burden is placed upon the

Applicants to establish a patentable distinction between the claimed and referenced products. The method in which the myoblasts were produced is immaterial to their patentability.

"Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP §2113.

In the instant claims, the claims recite "obtainable by culturing said myoblasts in a cell culture medium comprising serum of animal origin". Absent evidence to the contrary, the recitation "obtainable by...." is not considered to further limit the invention.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute the myoblast cell line of Chancellor et al with the primary myoblasts of Yiou et al with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. An artisan would be motivated to substitute an immortalized myoblast cell line for an autologous primary myoblast because the autologous primary myoblast would be expected to overcome immunological graft-vs.-host tissue rejection concerns as well as negate the potential formation of tumorous tissue arising from the implanted immortalized cells.

It also would have been obvious to modify the method of Chancellor et al or Yiou et al to comprise the culturing steps of performing cell differentiation before, during or after cell amplification, carrying out a functionality test on the suitability of the myoblasts for forming colonies, performing a characterization on said myoblasts and freezing the myoblasts because all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. An artisan would be motivated to combine the culturing steps to harvest,

separate, amplify, characterize and differentiate primary myoblasts so as to demonstrate that the cells extracted from primary muscle tissue and to be implanted into a subject in need possess the desired biological properties, thereby increasing the likelihood of successful therapeutic treatment. The artisan would also be motivated to cryopreserve the myoblasts for future use as needed by the patient's medical condition.

Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

Conclusion

7. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to KEVIN K. HILL whose telephone number is (571)272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill, Ph.D./
Examiner, Art Unit 1633

/Q. JANICE LI/
Primary Examiner, Art Unit 1633